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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/519,998	03/06/2000	D. Scott Wilbur	33700W003	8767

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EXAMINER	
KANTAMNENI, SHOBHA	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 01/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/519,998	WILBUR ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *25 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-9,11-22 and 24-40* is/are pending in the application.

4a) Of the above claim(s) *26-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6-9, 11-22, 24-25, 31-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 6-9, 11-22, and 24-40 are pending. Claims 4-5 are cancelled and claims 26-30 are withdrawn from consideration. The Amendments filed on 08/25/2004 amended claims 1, 14, 32 and added new claim 40.

Response to Applicant's Arguments/Amendment

Applicant's amendment to claim 1 by removing "for diagnosis and treatment of human and animal conditions or diseases" overcomes the rejection of claims 1-9, 11-22, 24-25, and 31-39 under 35 U.S.C. 112, first paragraph.

Applicant's argument over the term "a derivative of avidin or streptavidin" in claim 8 is sufficient enough to overcome the rejection of claim 8 under 35 U.S.C. 112, second paragraph.

Applicant's amendment to claims 14 and 32 overcomes the rejection of claims 14 and 32 under 35 U.S.C. 112, second paragraph as being indefinite.

In view of Applicant's amendments including cancellation of claims 4 and 5, the rejection of claims 1-9, 11-22, 25, 31-32, 34-39 under 35 U.S.C. 103(a) in the previous Office Action 06/03/2004 is herein withdrawn.

The Amendments to the claims necessitated the following new rejections.

Claim Objections

Claim 7 is objected to because of the following informalities: Claim 7 depends on claim 5, which has been cancelled by the Applicant. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being vague and indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 recites the limitation tetrafunctional in the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 40 is rejected because of the following:

(i) What does CHX-A" mean? Is it cyclohexyl-DTPA or something else? The specification does not define this abbreviation and one of ordinary skill in the art would not be apprised of its meaning.

(ii) The term "reagent comprises" is vague and indefinite, as the metes and bound of this claim is unascertainable. In claim 1 the reagent is defined as a single molecule. How can a single molecule comprise more compounds?

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 6-9, 11-13, 15-22, and 35-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 33, 34, 36, 38, 55-59, 62, 64-67, 70, 73-74, 88-89, and 98 of copending Application No. 09/750,280. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is no patentable distinction between the two sets of claims.

The proviso at the end of claim 1 of 09/519,998 avoids overlap. However, the claimed stabilizing moieties towards enzymatic cleavage of the biotinamide bond such as alpha carboxylate of '998' and the use of aspartyl moiety which results in beta carboxylate are homologues. It would have been obvious to one having ordinary skill in the art at the time the invention was made, to use alpha carboxylate in linker 1 of the affinity ligand because a homologous series is a family of chemically related compounds, the composition of which varies from member to member by CH_2 * * *, wherein Chemists knowing the properties of one member would in general know what to expect in adjacent members (In re Henze, 85 USPQ 261, 261 (CCPA 1950)); thus, one of skill in the art would have been motivated to teach "alpha carboxylate" as aspartyl moiety in linker 1 a) because of the expectation of achieving the same binding with avidin or streptavidin and b) because adjacent homologs are considered to be obvious variants absent unexpected results.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The instant invention is directed toward a reagent comprising a trifunctional cross-linking moiety, an affinity ligand, a biomolecule reactive moiety, an effector agent, and three optional linkers.

Claims 1-3, 6-9, 11-22, 24-25, 31-32, and 34-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilber et al. (WO 97/29114) and in view of Wilbur et al. (Bioconjugate Chem. 1997, 8, 572-584) or in view of Rosebrough (The Journal of Pharmacology and Experimental Therapeutics, vol 265, No.1, 1993, 408-415).

Wilbur et al. exemplify a trifunctional biotin reagent, wherein tricarboxybenzene is the trifunctional cross-linking moiety, biotin is the affinity ligand, maleimide is the biomolecule reactive moiety, an aryl iodide bonding moiety is the effector agent, and trioxadiamine (which contains 15 atoms) is the linker, wherein the affinity ligand is connected to the linker via a biotinamide bond. The linkers are connected to the individual components by amide bonds. The linkers contain ether groups which are hydrogen bonding atoms. Biotin binds with another molecule with an affinity constant of

10^6 M-1 or higher and specifically binds to avidin. See page 39. On page 18, Wilbur et al. teach carboxylate active esters of hydroxysuccinimidyl and phenyl as interchangeable with maleimides. On page 23, it is taught that EDTA, DTPA, DOTA and others may provide chelates for radionulcides such as Y-90. On page 6, biotin, desthiobiotin, biotin sulfone, and iminobiotin, are taught as interchangeable affinity ligands. On pages 9-10, it is taught that trifunctional cross-linkers can be utilized without linkers. Wilbur also teaches that the linker moiety attached to the biotin moiety is modified under certain conditions by introduction of a steric group such as carboxylates, larger alkyl groups, aryl groups etc. alpha to the amine (or another functionality) of the linker, to provide resistance to cleavage by biotindase. See page 17, lines 26-30; page18, lines 1-12. Wilbur '114 also teaches more than one affinity ligand and/or more than one effector agent attached to the trifunctional crosslinking group. See page 33, compound 50; page 28, compound 46.

The reference lacks an N-methyl group in linker 1. The reference further lacks an exemplification of excluding linkers 2 and 3, chelating groups, radionuclides, and preferred active esters.

Wilbur et al. (Bioconjugate) teach biotin reagents for antibody pretargeting, see title. It is taught that N-methyl containing moieties are added to the biotin moiety to block biotinidase activity, thereby increasing its stability against degradation, see abstract.

Rosebrough teaches the plasma stability and pharmacokinetics of radiolabeled deferoxamine-biotin derivatives, see title. IT is taught that the introduction of an alpha-

carboxylate group in the linker blocks biotinidase activity, thereby increasing the stability of biotin, see abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate an N-methyl group, as taught by Wilbur et al. (Bioconjugate), or an alpha-carboxylate group, as taught by Rosebrough, into the linker between biotin and tricarboxybenzene, of Wilbur et al., because of the expectation of achieving a reagent that blocks biotinidase activity, thereby increasing the stability of the reagent, as taught by Wilbur et al. (Bioconjugate) and Rosebrough.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute an ester of hydroxysuccinimidyl for the maleimide in structure 56 of Wilbur et al. because Wilbur et al. teach these biomolecule reactive moieties as interchangeable preferable compounds for conjugation to an activated biotinylation reagent.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the chelated radionuclides taught by Wilbur et al. on page 23 of the specification for the amino carboxy containing radionuclide because of the expectation of achieving similar radiotherapeutic effects and because of the expectation of achieving a radionuclide that is stabilized.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute biotin sulfone for biotin in structure 56 of Wilbur et al. because Wilbur et al. teach these biotins as interchangeable affinity ligands.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to teach structure 56 without linkers 2 and/or 3 because Wilbur et al. teach that linkers are not necessary and because of the expectation of achieving a compound that is stabilized from its medium, as it is not as reactive with it.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute homobiotin or norbiotin for the biotin taught by Wilbur et al. because adjacent homologs are considered to be obvious absent unexpected results. *In re Henze*, 85 USPQ 261, 263 (CCPA 1950).

It is respectfully pointed out that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. *See In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Thus, limitations drawn to the intended use of the instant reagent have not been given patentable weight, i.e., "forming a covalent bond between the reagent and the biomolecule".

Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wilbur et al. in view of Wilbur et al. or in view of Rosebrough as applied to claims 1-3, 6-9 11-22, 24-25, 31-32, 34-39 above, and further in view of Gansoh et al. (5,286,850).

Wilbur et al. is applied as discussed above. The reference lacks preferred DTPA.

Gansoh et al. teach cyclohexyl DTPA as a radioactive ligand for radioimaging.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute cyclohexyl DTPA as taught by Gansoh et al. for DTPA in the invention of Wilbur et al. because of the expectation of achieving similar chelating effects and better chelating effects when an antibody is bound to the chelator. Furthermore, it is within the skill of an artisan in the contrast agent art to substitute one chelating agent for another.

Response to Arguments

Applicant argue's "Applicants again submit that the cited documents do in no way teach or fairly suggest introducing an N-methyl group or alpha carboxylate into linker 1 to thereby stabilize linker 1 against enzymatic cleavage.. ...In addition, Applicants also submit herewith a Declaration signed by Dr. D. Scott Wilbur that explains that those of ordinary skill in the art would not interpret the cited documents as teaching or even suggesting employing an N-methyl group or alpha carboxylate in a trifunctional reagent". This argument is not persuasive. Wilbur '114 teaches a trifunctional reagent comprising tricarboxybenzene as the trifunctional cross-linking agent, biotin as the affinity ligand, maleimide as the biomolecule reactive moiety, iodinated benzene as the effector agent, and trioxadiamine as linker 1, linker 2, and linker 3. Wilbur also teaches that the linker moiety attached to the biotin moiety is modified under certain conditions by introduction of a steric group such as carboxylates, larger alkyl groups, aryl groups etc. alpha to the amine (or another functionality) of the linker, to provide resistance to cleavage by biotindase. See page 17, lines 26-30; page18, lines 1-12; and pages 38-39.

Applicant argue's "Rosenborough fails to prove that carboxylate in the cysteine linker plays a role in blocking biotinidase cleavage". This argument is not persuasive. Rosenborough teaches that Defero-acetyl-cysteinyl-biotin (DACB) was designed to reduce the enzymatic degradation by incorporating a COO^- group adjacent to the amide bond cleavage site in the spacer arm separating deferoxamine and biotin. See The Journal of Pharmacology and Experimental Therapeutics, Vol 265, No.1, 1993, 408-415 page 414, bottom right paragraph. Thus Rosenborough suggests the use of alpha-carboxylate to reduce the enzymatic cleavage biotinamide bonds.

Applicant argue's "even if others of skill in the art had made the assumption that an alpha-carboxylate was responsible for blocking biotinidase cleavage of biotinamide bonds, and had been taught that an N-methyl blocked biotinidase cleavage from Dr. Wilbur's paper, the combination of this knowledge would not adequately teach or suggest the claimed invention. Dr. Wilbur goes on to explain that there are two important and interactive factors in the biotin derivatives for applications....One of them is the requirement for very high biotinidase stability. The second factor is that biotin derivatives used must retain a very high binding affinity...The claimed invention includes these two very important functional aspects". This argument is not persuasive because (i) it is not commensurate in scope with the instant claims. The Examiner respectfully points out that the instant claims are directed to a compound. Thus, since Wilbur teaches the same compound as that of the instant invention, for the same use, Wilbur teaches the limitations of the instant claims and does not need to suggest any core guidelines of Applicants' invention, since a compound and its properties are inseparable

(ii) Wilbur '114 does teach that biotin is useful for many different applications as a result of its strong binding affinity for avidin or streptavidin. See page 6, lines 2-4. Wilbur also teaches that depending on the particular application of the biotin compound a variety of biotin moieties with carboxylate coupled steric moieties and water soluble linker moiety a single molecule reagent having varying binding affinities and enhanced resistance to serum enzyme biotinidase are provided. See Page 18, lines 10-13. Thus the combined references teach the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER